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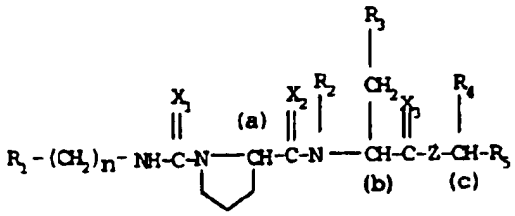

(I)

(57) Abstract

Compounds of formula (I), wherein R_1 is mono- or di-substituted phenyl, n is zero or 1, X_1 is oxygen, sulfur or =NCN, X_2 and X_3 are oxygen or sulfur, R_2 is hydrogen or methyl, R_3 is phenyl, halo-substituted phenyl, 2-naphthyl, IH-indol-3-yl or 1-methyl-indol-3-yl, Z is $-N(CH_3)-$ or $-CH_2-$, R_4 is phenyl, 3,5-bis(trifluoromethyl)phenyl or pyridyl and R_5 is hydrogen, phenyl 3,5-bis(trifluoromethyl)phenyl or pyridyl, whereby, when X_3 is sulfur, Z is $-N(CH_3)-$ and acid addition salt thereof have tachykinin antagonist activity and are useful as pharmaceuticals, e.g. for the treatment of pain.

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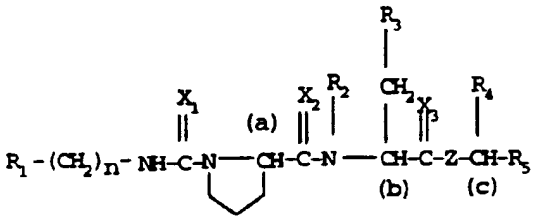
TACHYKININ ANTAGONISTS

The present invention relates to novel compounds having tachykinin antagonist activity, processes for their production, pharmaceutical compositions comprising them and their use as pharmaceuticals or pharmaceutical use.

More particularly the present invention provides in a first aspect, a compound of formula I



(I)

wherein

R_1 is phenyl mono- or di-substituted by one or two members selected from the group consisting of halogen, nitro, cyano, trifluoromethyl, hydroxy, methoxy, hydroxymethyl, methoxymethyl, methoxycarbonyl, carbamoyl and N-methyl-carbamoyl,

n is zero or 1,

X_1 is oxygen, sulfur or =NCN,

X_2 and X_3 are each independently oxygen or sulfur,

R_2 is hydrogen or methyl,

R_3 is phenyl, halo-substituted phenyl, 2-naphthyl, IH-indol-3-yl or 1-methyl-indol-3-yl,

Z is $-N(CH_3)-$ or $-CH_2-$,

R_4 is phenyl, 3,5-bis(trifluoromethyl)phenyl or pyridyl and

R_5 is hydrogen, phenyl 3,5-bis(trifluoromethyl)phenyl or pyridyl,

whereby, when X_3 is sulfur, Z is $-N(CH_3)-$,

or acid addition salt thereof.

By halogen (and halo) is meant chlorine (chloro), fluorine (fluoro), bromine (bromo) and iodine (iodo).

When R_1 is di-substituted phenyl the substituents may be the same or different.

1. In a group of compounds of formula I R_1 is phenyl mono- or di-substituted by one or two members selected from the group consisting of nitro, cyano, trifluoromethyl, hydroxymethyl, methoxymethyl, carbamoyl and N-methylcarbamoyl.
2. In a further group of compounds of formula I in accordance with the present invention n is zero.
2a. When n is zero, R_1 is preferably phenyl mono- or di-substituted by one or two members selected from the group consisting of nitro, cyano, methoxymethyl, methoxycarbonyl, carbamoyl and N-methylcarbamoyl (e.g. nitro, cyano, methoxymethyl, carbamoyl and N-methylcarbamoyl) especially nitro and methoxymethyl, most especially nitro.
2b. When n is zero, R_1 is preferably mono-substituted phenyl, in particular phenyl mono-substituted at the 2-position.
2c. When n is zero, R_1 is most preferably phenyl mono-substituted at the 2-position by any of the substituents set forth under 2a above, in particular 2-nitrophenyl and 2-(methoxymethyl)phenyl, especially 2-nitrophenyl.
3. In a yet further group of compounds in accordance with the present invention n is 1.
3a. When n is 1, R_1 is preferably phenyl mono- or di-substituted by one or more members selected from the group consisting of halogen, trifluoromethyl, and methoxy, especially halogen and trifluoromethyl.
3b. When n is 1, R_1 is preferably phenyl mono-substituted at the 2-position or di-substituted at the 2- and 6-position.
3c. When n is 1, R_1 is most preferably phenyl mono-substituted at the 2-position or di-substituted at the 2- and 6-position by any of the substituents set forth under 3a above, especially phenyl mono-substituted at the 2-

position, in particular 2-halo- or 2-trifluoromethylphenyl, especially 2-chloro- or 2-trifluoromethylphenyl and most especially 2-chlorophenyl.

In the compounds of formula I

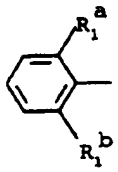
4. Preferably n is zero.
5. Preferably X_1 is oxygen or sulfur, especially oxygen.
6. Preferably X_2 and X_3 are each oxygen.
7. Conveniently R_2 is hydrogen.
8. When R_3 is halo-subsituted phenyl this is suitably di-halo-substituted phenyl, in particular 3,4-di-halosubstituted phenyl. Preferred as halo is chloro, 3,4-di-chlorophenyl being particularly suitable as R_3.
9. Preferably R_3 is 2-naphthyl or halo-substituted phenyl, e.g. as defined under 8 above, in particular 2-naphthyl.
10. Z is preferably $-N(CH_3)-$.
11. When R_5 is other than hydrogen R_4 and R_5 are suitably the same.
12. Pyridyl as R_4 and/or R_5 is preferably 2-pyridyl.
13. Preferably R_4 is phenyl.
14. Preferably R_5 is hydrogen.
15. Most preferably R_4 is phenyl and R_5 is hydrogen.

The present invention is to be understood as embracing compounds of formula I in which the meanings of the substituents R_1 to R_5, X_1 to X_3, n and Z comprise any combination or sub-combination of the meanings given under formula I and/or under any one or more of paragraphs 1 through 15 above.

A. In a sub-group of compounds in accordance with the present invention
R_1 is 2-halo- or 2-nitro-phenyl,
n is zero,
X_2 and X_3 are each oxygen,
R_4 is phenyl or pyridyl,
R_5 is hydrogen, phenyl or pyridyl and

X_1, R_2, R_3 and Z have the meanings hereinbefore given for formula I.

B. In a further sub-group of compounds in accordance with the present invention
R_1 is a group of formula



wherein R_1^a is trifluoromethyl, halogen, methoxy or nitro and
R_1^b is hydrogen, trifluoromethyl, halogen, methoxy or nitro,
n is 1,
X_2 and X_3 are each oxygen,
R_3 is halo-substituted phenyl, 2-naphthyl, IH-indol-3-yl, or 1-methyl-indol-3-yl,
Z is $-N(CH_3)-$ and
X_1, R_2, R_4 and R_5 have the meanings hereinbefore given for formula I

Preferred significances in relation to the sub-groups defined under A and B above are as indicated under paragraphs 1 through 15 above.

Compounds of formula I in which R_4 and/or R_5 is pyridyl exist in free form and in acid addition salt form. The present invention is to be understood as including both the free compounds of formula I and their acid addition salts. Suitable pharmaceutically acceptable acid addition salts for use in accordance with the present invention include e.g. hydrochloride salts.

Compounds of the invention comprise two asymmetric carbon atoms

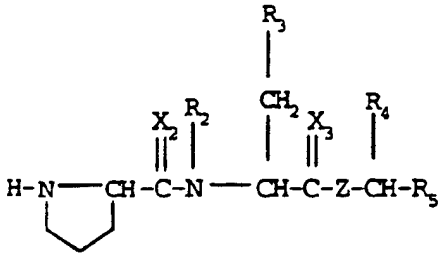
[marked (a) and (b) in formula I]. When R_4 and R_5 are different and R_5 is other than hydrogen, a further asymmetric carbon atom [(c)] is present. The compounds accordingly exhibit optical isomerism.

Individual isomers may be obtained in conventional manner, e.g. by synthesis using optically active starting materials or by separation of initially obtained isomeric mixtures, for example employing chromatographic techniques using a chiral support or by recrystallisation of diastereomeric salt forms.

The present invention is to be understood as embracing both individual isomers in pure or substantially pure form as well as mixtures, e.g. racemic and diastereomeric mixtures, unless otherwise specified.

In formula I each of the carbon atoms (a) and (b) preferably has the (S)-configuration. More preferably both carbon atoms (a) and (b) have the (S)-configuration. Accordingly, in a preferred aspect the present invention provides a compound of formula I as hereinbefore defined wherein the carbon atoms (a) and (b) both have the (S)-configuration in pure or substantially pure form, e.g. comprising less than 10%, more preferably less than 5%, e.g. less than 2% of other isomeric forms.

The present invention further provides a process for the production of a compound of formula I as hereinbefore defined or acid addition salt thereof, which process comprises reacting a compound of formula II



(II)

wherein R_2 to R_5, X_2, X_3 and Z have the meanings hereinbefore given, with a compound of formula III

$$R_1'-(CH_2)_n-N=C=X_1 \qquad (III)$$

wherein R_1' is phenyl, mono- or di-substituted by one or two members selected from the group consisting of halogen, nitro, cyano, trifluoromethyl, protected hydroxy, methoxy, protected hydroxymethyl, methoxymethyl or methoxycarbonyl, and n and X_1 have the meanings given for formula I;
when required, deprotecting a compound thus obtained wherein R_1' is phenyl substituted by protected hydroxy and/or protected hydroxymethyl and/or transforming a compound thus obtained wherein R_1' is phenyl substituted by methoxycarbonyl to obtain a corresponding compound wherein R_1' is phenyl substituted by carbamoyl or N-methylcarbamoyl;
and recovering the obtained compound of formula I in free or acid addition salt form.

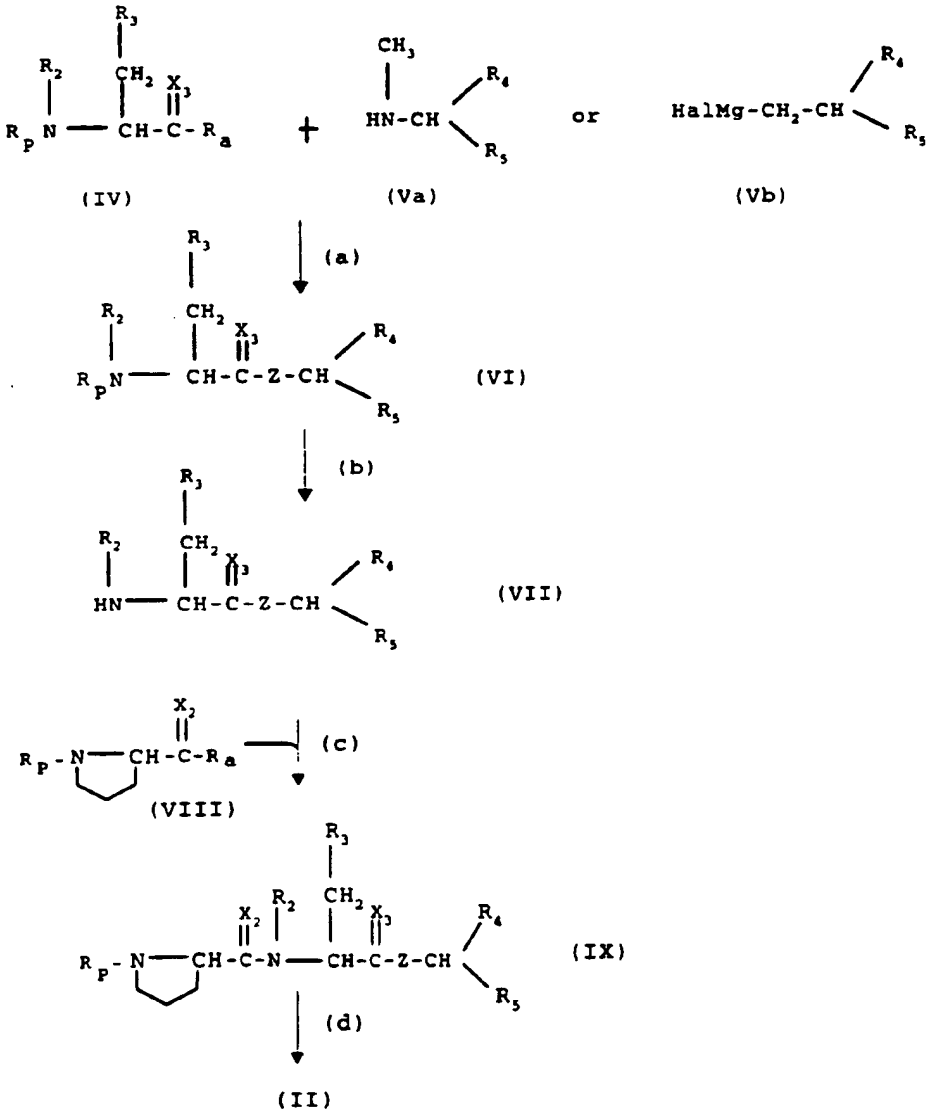
Reaction of compounds II with III is suitably performed in an inert organic medium, e.g. dioxane, at temperatures of from 20° C to reflux.

Protecting groups of protected hydroxy or hydroxymethyl moieties comprising R_1' may be any oxy-protecting group as known and commonly employed in the art of peptide chemistry, for example, t.butyldimethylsilyloxymethyl. Deprotection may be carried out in accordance with standard procedures, e.g. as hereinafter described in relation to EXAMPLES 18 and 19.

Transformation of methoxycarbonyl moieties may also be carried out in accordance with standard procedures as known in the art, e.g. by hydrolysis to carboxy, conversion of the carboxy moiety to a reactive functional derivative, e.g. carbonylhalide or mixed anhydride moiety, and reaction of this with ammonia or methylamine, e.g. as hereinafter described in relation to EXAMPLES 15 and 16.

Starting materials of formula III are known from the art, commercially available or producible analogously to the known compounds, e.g. in the case of compounds of formula III wherein X = =NCN in accordance with the general procedures hereinafter described in relation to EXAMPLE 4.

Compounds of the formula II may be prepared according to the following reaction sequence:



in which R_p represents an amino protecting group, R_a represents a carboxy activating group, Hal is chlorine, bromine or iodine, especially bromine, and R_2 through R_5, X_2, X_3 and Z have the meanings hereinbefore given.

Suitable amino protecting groups as R_p include any of those known and employed in the art of peptide synthesis, t-butoxcarbonyl (Boc) being, for example, particularly suitable in relation to formulae (IV) and (VIII).

Reaction of compounds IV with Va and Vb leads to compounds VI (and hence II) in which Z = $-N(CH_3)-$ and $-CH_2-$ respectively.

Suitable carboxy activating groups R_a for reaction of IV with Va as well as process step (c) include mixed anhydride activating groups, e.g. i-butoxycarbonyloxy. Reaction may be performed in accordance with any of the techniques known and employed in the art of peptide chemistry, e.g. in accordance with the general methods of EXAMPLE 1A.2.

Starting materials of the formula Va and Vb are known from the art or may be prepared analogously to known compounds, e.g. as hereinafter illustrated in relation to EXAMPLES 5, 20 and 24.

Suitable carboxy activating groups R_a for reaction of IV with Vb include pyridyl and picolyl ester groups, e.g. 2-pyridyloxy. Reaction may be carried out in accordance with procedures known in the art with formation of the Grignard reagent Vb in situ, for example as hereinafter described in relation to EXAMPLE 28.

Starting materials of formula IV are known or described in the art or may be produced according to known procedures, for example by activation of the corresponding N-protected acids, suitably in situ, for example as hereinafter described in EXAMPLE 1A.1.

Alternatively, compounds of formula II wherein R_2 is methyl may be produced proceeding from compounds of formula IV wherein R_2 is

hydrogen and carrying out an intermediate methylation, e.g. of the compound of formula IX prior to step (d), according to the method of Olsen, J.Org. Chem., 35, 1912-1915 (1970). This approach is illustrated in relation to EXAMPLES 27 and 29.

Process steps (b) and (d) are conventional de-protection steps as commonly practiced on the art of peptide synthesis e.g. as hereinafter illustrated in EXAMPLE IB.

The following examples are illustrative of the processes for the production of the compounds of the invention.

EXAMPLE 1:

Preparation of 2-nitrophenylcarbamoyl-[(S)-prolyl]-[(S)-3-(2-naphthyl)alanyl]-N-benzyl-N-methylamide:

[Formula I: R_1 = 2-nitrophenyl; n = zero; X_1, X_2 and X_3 each = oxygen; R_2 = H; R_3 = 2-naphthyl, Z = $-N(CH_3)-$; R_4 = phenyl and R_5 = H; both carbon atoms (a) and (b) have the (S)-configuration.]

To (S)-prolyl-(S)-3-(2-naphthyl)alanyl-N-benzyl-N-methylamide (1.39g) in ethyl acetate (15ml) are added 2-nitrophenylisocyanate (551 mg). The yellow solution is stirred at room temperature for 1 hour. The reaction mixture is concentrated. The orange residue is purified by flash chromatography (2:1 ethylacetate: hexane) to afford a yellow foam. The foam is dissolved in ethyl acetate (20ml) and dropped slowly into a stirred solution of hexane (200ml). The yellow precipitate is filtered and dried to yield the title compound: m.p. = 79-82°C; TLC (silica, cyclohexane/ethyl acetate 1:2) Rf = 0.36.

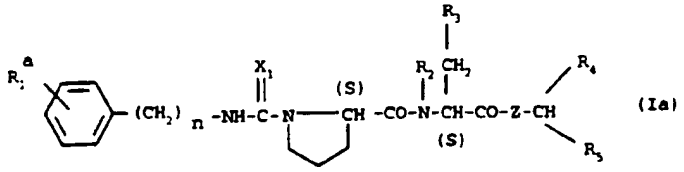
EXAMPLE 2:

Preparation of 2-chlorobenzothiocarbamoyl-[(S)prolyl]-[(S)-3-(2-naphthyl)alanyl]-N-benzyl-N-methylamide.

[Formula I: R_1 = 2-chlorophenyl; n = 1; X_1 = sulfur; X_2 and X_3 each = oxygen; R_2 = H; R_3 = 2-naphthyl; Z = $-N(CH_3)-$; R_4 = phenyl and R_5 = H; both carbon atoms (a) and (b) have the (S)-configuration.]

(S)-Prolyl-(S)-3-(2-naphthyl)-alanyl-N-benzyl-N-mehtylamide (1.03g) is dissolved in 10ml CH_2Cl_2 with 2-chlorobenzyl isothiocyanate (455mg), and the solution is stirred at room temperature for 18 hours. The solvent is removed in vacuo. The product is purified by flash column chromatography (silica, cyclohexane/ethyl acetate 1:2) and crystallised from ethyl acetate, to give fine white needles. These are filtered, and dried at 0.1mmHg/75°C for 18 hours to yield the title compound: m.p. = 129-131°C,: TLC (silica, cyclohexane/ethyl acetate 1:2) Rf=0.3.

The following compounds of formula Ia



(Ia)

wherein R_2 is hydrogen, R_3 is 2-naphthyl and Z is $-N(CH_3)-$ may be prepared analogously to example 1 (when n = zero) or example 2 (when n = 1) above.

EXAMPLE	R_1*	n	X_1	R_4	R_5	Physical Data m.p.(°C)/Rf.
3	$2NO_2$-	zero	S	phenyl	H	118-121 / 0.45[1]
4*	$2NO_2$-	zero	=NCN	phenyl	H	92-96 / 0.10[1]
5	$2NO_2$-	zero	O	2-pyridyl	2-pyridyl	90-92 / 0.18[3]
6	$2NO_2$-	zero	O	2-pyridyl	H	69-71 / 0.01[3]

EXAMPLE	R_1*	n	X_1	R_4	R_5	Physical Data m.p.°C / Rf.
7	$2NO_2$-	zero	S	2-pyridyl	H	98-100 / 0.01[3]
8	2Cl-	zero	S	phenyl	H	94-98 / 0.04[1]
9	$4NO_2$-	zero	O	phenyl	H	126-129 / 0.20 [1]
10	2CN-	zero	O	phenyl	H	124-126 / 0.25 [1]
11	3CN-	zero	O	phenyl	H	105-107 / 0.15[1]
12	4F-	zero	O	phenyl	H	85-87 / 0.28 [1]
13	$2(CH_3OCO)$-	zero	O	phenyl	H	50-60 / 0.23 [1]
14	$3NO_2$-	zero	O	phenyl	H	98-101 / 0.25 [1]
15**	$2(CH_3NHCO)$-	zero	O	phenyl	H	96-102 / 0.19 [2]
16**	$2(NH_2CO)$-	zero	O	phenyl	H	109-115 / 0.10 [2]
17	$2(CH_3OCH_2)$-	zero	O	phenyl	H	58-62 / 0.27 [1]
18***	2HO-	zero	O	phenyl	H	98-104 / 0.24 [1]
19***	$2(HOCH_2)$-	zero	O	phenyl	H	83-86 / 0.20 [2]
20	2Cl-	1	S	2-pyridyl	2-pyridyl	95-97 / 0.09[3]
21	2Cl-	1	S	2-pyridyl	H	85-87 / 0.01[4]
22	$2CF_3$-	1	S	phenyl	H	175-176/ 0.19[1]
23	2Cl-	1	O	phenyl	H	69-73 / 0.18[1]
24	2Cl-	1	S		H	125-127 / 0.11[4]
25	2Cl-	1	S	phenyl	phenyl	102-104 / 0.15[4]
26	2Br-	1	S	phenyl	H	142-143 / 0.45 [1]

The following compounds of formula Ia above wherein R_1* is $2NO_2$-, R_3 is 2-naphthyl, R_4 is phenyl and R_5 is H may be prepared

analogously to example 1 (when n = zero) or example 2 (when n = 1) above.

EXAMPLE	n	X_1	R_2	Z	Physical Data m.p.°C/Rf.
27	zero	O	CH_3-	-N(CH_3)-	71-74/ 0.55[2]
28	zero	O	H	-CH_2-	106-108/0.35[4]
29	1	S	CH_3-	-N(CH_3)-	84-85/ 0.19[4]

The following compounds of formula Ia above wherein R_2 is hydrogen, Z is -N(CH_3)-, R_4 is phenyl and R_5 is hydrogen may be prepared analogously to example 1 (when n = zero) or example 2 (when n = 1) above:

EXAMPLE	R_1*	n	X_1	R_3	Physical Data m.p.°C/Rf.
30	2NO_2-	zero	O	IH-indol-3-yl	96-98/ 0.36[2]
31	2NO_2-	zero	O	3,4-dichlorophenyl	151-152/0.54[2]
32	2Cl-	1	S	3.4-dichlorophenyl	185-186/0.59[2]
33	2Cl-	1	S	I-methylindol-3-yl	160-162/0.06[4]

(1) = Silica, cyclohexane/ethyl acetate 1:2
(2) = Silica, cyclohexane/ethyl acetate 1:4
(3) = Silica, CH_2Cl_2/CH_3OH 25:1
(4) = Silica, cyclohexane/ethyl acetate 1:1

* For the preparation of the EXAMPLE 4 compound the starting material of formula III is prepared in situ as follows:

Potassium t-butoxide (1ml, 1M in tetrahydrofuran) is added to cyanamide (44mg) in dimethyl formamide (5ml). A white precipitate forms. The reaction mixture is stirred for 20 mins. at room temperature. 2-Nitrophenyl isothiocyanate (180mg) is added as a

solid and the reaction mixture is stirred for 10 mins. at room temperature. The mixture is cooled in ice and triethylamine (0.42ml) added followed by (S)-prolyl-(S)-3(2-naphthyl)alanyl-N-benzyl-N-methylamide (415 mg) and $HgCl_2$ (300mg). Further reaction and work-up then proceeds according to example 1.

** The compounds of EXAMPLES 15 and 16 are prepared via the compound of EXAMPLE 13 employing the following additional steps:

The product of EXAMPLE 13 is hydrolysed to provide the corresponding acid in which R_1^a (formula Ia) = 2(HOCO)-. The acid is then reacted with isobutyl chloroformate and N-methylmorpholine in ethyl acetate under standard conditions (temperature maintained below -15°C) whilst dry methylamine (for the production of the compound of EXAMPLE 15) or ammonia gas (for the production of the compound of EXAMPLE 16) is slowly introduced into the reaction vessel over a period of 30 minutes. The obtained raw products are worked up analogously to the procedures described in EXAMPLE 1.

*** The compounds of EXAMPLES 18 and 19 are prepared via an O-protected intermediate, e.g. as follows:

(S)-prolyl-(S)-3-(2-naphthyl)-alanyl-N-benzyl-N-methyl-amide is reacted with 2-(t.butyldimethylsilyloxy)phenyl isocyanate/2-(t.butyldimethylsilyloxymethyl)phenyliso-cyanate analogously to EXAMPLE 1 to yield the EXAMPLE 18 and 19 compounds respectively in t.butyldimethylsilyl-protected form. Deprotection to yield the EXAMPLE 18 and 19 compounds is effected under standard conditions employing tetrabutyl ammonium fluoride in tetrahydrofuran.

The starting material for the process of EXAMPLE 1 is prepared as follows.

EXAMPLE 1A [Process step (a)]

1A.1 Preparation of Boc-(S)-3-(2-naphthyl)alanine isobutoxy-formyl anhydride (Formula IV; R_p = Boc, R_2 = H, R_3 = 2-naphthyl, X_3 = O, R_a = i-butoxycarbonyloxy)

Boc-(S)-3-(2-naphthyl)alanine (480mg) is dissolved in 5ml dry CH_2Cl_2 with N-methyl morpholine (170µl, 156mg) and cooled with stirring under N_2 to -15°C, on a salt/ice bath. i-Butylchloroformate (200µl, 20mg) in 2ml dry CH_2Cl_2 is added dropwise, ensuring that the temp. remains below -10°C, and the reaction is stirred for 30 minutes.

1A.2. Preparation of Boc-(S)-3-(2-naphthyl)alanyl-N-benzyl-N-methylamide (Formula VI; R_p = Boc, R_2 = H, R_3 = 2-naphthyl, X_3 = O, Z = -N(CH_3)-, R_4 = phenyl, R_5 = H)

N-benzylmethylamine (Formula Va) (185mg) is added dropwise in 2ml dry CH_2Cl_2 to the product from EXAMPLE 1A.1, again ensuring that the temperature remains below -10°C, and the reaction is stirred until complete by TLC. The reaction is diluted to 75ml with CH_2Cl_2 and washed with 50 ml dilute aqueous HCl, 50ml water, and 25ml brine. The organic phase is dried over $MgSO_4$, filtered and the solvent removed in vacuo. The product is purified by flash column chromatorgraphy (silica, cyclohexane/ethyl acetate 4:1), to yield the title compound as a colourless foamed solid: TLC (silica, cyclohexane/ethyl acetate 1:1) Rf = 0.54.

EXAMPLE 1B [Process step (b)]

Preparation of (S)-3-(2-naphthyl)alanyl-N-benzyl-N-methylamide (Formula VII)

The product of EXAMPLE 1A (600mg) is dissolved in 10ml 4.0M HCl in dioxan, and stirred at room temperature for ca. 30 minutes. The HCl and dioxan are removed in vacuo, and the residue dissolved in 100ml water, basified with 2M NaOH(aq.), and extracted with CH_2Cl_2 (2x75ml). The organic phase is dried over $MgSO_4$, filtered and the solvent removed in vacuo, to give the

title compound as a yellow oil: TLC (silica, $CH_2Cl_2/CH_3OH/CH_3COOH$ 90:9:1) Rf = 0.43.

EXAMPLE 1C [Process step (c)]

Preparation of Boc-(S)-prolyl-(S)-3-(2-naphthyl)alanyl-N-benzyl-N-methylamide (Formula IX; R_p = Boc)

The title compound is prepared analogously to EXAMPLE 1A.2 by reaction of Boc-(S)-proline (310mg) with the product of EXAMPLE 1B (460 mg) and is obtained as a viscous oil: TLC (silica, cyclohexane/ethyl acetate 1:1) Rf = 0.18.

EXAMPLE 1D [Process step (d)]

Preparation of (S)-prolyl-(S)-3-(2-naphthyl)alanyl-N-benzyl-N-methylamide (Formula II)

The title compound is prepared analogously to EXAMPLE 1B starting from the product of EXAMPLE 1C (740mg) and is obtained as a colourless foamed solid: TLC (silica, $CH_2Cl_2/CH_3OH/CH_3COOH$ 90:9:1) Rf = 0.29.

The product of EXAMPLE 1D is also used as starting material for the production of the compounds of EXAMPLES 2 to 4, 8 to 19, 22, 23 and 26 and the starting materials of formula II for EXAMPLES 6, 7, 21, 25, and 30 to 33 are produced analogously.
The starting materials of formula II for EXAMPLES 5, 20, 24 and 27 to 29 are produced analogously to EXAMPLES 1A to 1D employing the following means to obtain the formula Va starting material and/or adaptations in procedure:

IN RELATION TO EXAMPLES 5 AND 20:

Preparation of N-methyl-(di-2-pyridyl)methylamine (Formula Va, R_4 and R_5 both = 2-pyridyl)

Di-2-pyridylketone (2.00g) is dissolved in 20 ml of CH_2Cl_2. Heptamethyldisilazan (1.90g) is added followed by trimethylsilyl trifluoromethanesulphonate (0.12g) and the reaction mixture is refluxed for 12 hours. The solvent is removed in vacuo. The crude oil (2.14g) is dissolved in 20 ml of dry C_2H_5OH. 0.65 g acetic acid is added followed by sodium cyanoborohydride (0.68g) and the reaction mixture is stirred at room temperature for 1 hour. A 1% solution of $KHSO_4$ is added until the solution is at pH 2 and then a 2M solution of NaOH is added until the solution is at pH 12. The C_2H_5OH is removed in vacuo and the product extracted into ethyl acetate. The organic layer is dried over $MgSO_4$, filtered and HCl is bubbled through the filtrate. The obtained title compound in trihydrochloride salt form is filtered off and dried for direct further reaction analogously to EXAMPLES 1A through 1D.

IN RELATION TO EXAMPLE 24:

Preparation of N-methyl-3,5-bis(trifluoromethyl)benzylamide [Formula Va: R_4 = 3,5-bis(trifluoromethyl)phenyl, R_5 = H

STEP I N-Boc-3,5-bis(trifluoromethyl)benzylamine

3,5-bis(trifluoromethyl)benzylamine (5.00g) and N-(benzyloxycarbonyloxy)succinimide (5.12g) are dissolved in 50ml of tetrahydrofuran and the reaction mixture is stirred at room temperature for 3 hours. The solvent is removed in vacuo and the product dissolved in CH_2Cl_2. The solution is washed with 50ml H_2O and 50ml brine. The organic layer is dried over $MgSO_4$, filtered and the solvent removed in vacuo to yield the title compound.

STEP II N-Boc-N-methyl-3,5-bis(trifluoromethyl)-benzylamine

The product of STEP II above (6.87g) is dissolved in 50ml of dry tetrahydrofuran and cooled to -78°C. 1.5M LDA in

tetrahydrofuran (14ml) is added the reaction mixture is stirred at -78°C for 30 minutes and 2.98g of methyl iodide is then slowly added. The reaction mixture is stirred at room temperature for 18h. The solvent is removed in vacuo and the product purified by flash column chromatography (silica, cyclohexane/ethyl acetate 9:1), to yield the title compound.

STEP III N-methyl-N-3,5-bis(trifluoromethyl)benzylamine

2.00g of the product of STEP III above is dissolved in 100ml of C_2H_5OH and deprotected by adding a catalytic amount of 10% palladium on charcoal and placing the solution under an atmosphere of hydrogen. The catalyst is filtered off after 4 hours and the solvent removed in vacuo. The obtained title compound is reacted further analogously to EXAMPLES 1A through 1D.

IN RELATION TO EXAMPLES 27 AND 29:

Preparation of Boc-(S)-prolyl-(S)-(N-methyl)-3-(2-naphthyl)-alanyl-N-benzyl-N-methylamide (Formula IX: R_p = Boc, R_2 = $-CH_3$, R_3 = 2-naphthyl, Z = $-N(CH_3)-$, R_4 = phenyl, R_5 = H)

The product of EXAMPLE 1C (1.08g) and iodomethane (1.04 ml, 2.38g) are dissolved in 30 ml dimethyl-formamide. Silver oxide (1.95g) is added, the reaction mixture is heated to 60°C and stirred until no starting material remains as determined by analytical HPLC. The reaction mixture is cooled to room temperature, diluted to 200ml with $CHCl_3$ and washed with 2x 100ml 5% KCN (aq.), 2 x 100ml H_2O and 50 ml brine, then dried over anhydrous $MgSO_4$, filtered and the solvent removed in vacuo to yield the title compound as a pure colourless glass.

The title compound is reacted further analogously to EXAMPLE 1D.

IN RELATION TO EXAMPLE 28:

28.A.1. Preparation of Boc-(S)-3-(2-naphthyl)alanine 2-pyridyl ester (Formula IV : R_p = Boc, R_2 = H, R_3 = 2-naphthyl, R_6 = 2-pyridyloxy)

Boc-(S)-3-(2-naphthyl)alanine (1.00g) and 2-hydroxypyridine (0.33g) are dissolved in 5ml of dry pyridine and the solution cooled to 0°C. Dicyclohexylcarbodiimide (0.72g) is added and the reaction mixture stirred at 0°C for 6 hours. The solvent is removed in vacuo and the product dissolved in 20ml of ethyl acetate, filtered and the solvent removed in vacuo. The product is purified by flash column chromatography (silica, cyclohexane/ethyl acetate, 2:1), to yield the title compound: TLC (silica, cyclohexane/ethyl acetate 1:1) Rf = 0.41.

28.A.2. Preparation of Boc[1-(S)-naphthalen-2-yl-methyl-2-oxo-4-phenyl-butyl]amine [Formula VI: R_p = Boc, R_2 = H, R_3 = 2-naphthyl, Z = $-CH_2-$, R_4 = phenyl, R_5 = H]

The product of EXAMPLE 29.A.1. (0.85g) is dissolved in 10ml of dry tetrahydrofuran in a flame-dried flask, and the solution is stirred under nitrogen. The solution is cooled to -78°C and a 2M solution of phenethylmagnesium bromide (2ml) is slowly added. The reaction mixture is stirred at -78°C for 1 hour. 20ml of saturated ammonium chloride solution is added and the product extracted into ethyl acetate. The organic layer is dried over $MgSO_4$, filtered and the solvent removed in vacuo. The product is purified by flash column chromatography (silica, cyclohexane/ ethyl acetate 9:1) to give the title compound: TLC (silica, cyclohexane /ethyl acetate 4:1) Rf = 0.66.

The title compound is processed further analogously to EXAMPLES 1B through 1D.

For larger scale production, the reaction procedures of EXAMPLES 1A through 1 may appropriately be adapted as indicated in the

following EXAMPLE 34.

EXAMPLE 34:

Large scale preparation of 2-nitrophenylcarbamoyl-[(S)-prolyl]-[(S)-3-(2-naphthyl)alanyl]-N-benzyl-N-methylamide:

STEP I (= EXAMPLE (A)

A 0.5-L, 3-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet-outlet, and cooling bath is charged with 187,4g of N-benzylmethylamine and cooled to 1-5°C (internal temperature). 7.5g of ethyl trifluoroacetate are added dropwise over a period of 15 minutes while maintaining an internal temperature of 1-5°C. The funnel is washed with a total of 7.5ml of ethyl acetate in three equal portions of 2.5ml each and the reaction mixture is added. The cooling bath is removed and the mixture warmed to room temperature (21-23°C) in 30 min. The mixture is stirred at room temperature for 30 min. and the oil held.

A 12-L, 4-necked, round-bottomed flask, equipeed with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet-outlet, and cooling bath is charged with 394,0g of Boc-(S)-3-(2-naphthyl)alanine, and 5,6L of ethyl acetate. The solution is cooled to -15°C (internal temperature) and 174,4g of 4-methylmorpholine are added over a period of 5 minutes. The addition funnel is washed with 25ml of ethyl acetate and this is added to the reaction mixture. The mixture is stirred for 10 minutes and a solution of 172.0ml (181.12g) of isobutyl chloroformate in 125ml of ethyl acetate is added over a period of 30 minutes while maintaining an internal temperature of -14 to -16°C. The addition funnel is washed with 50ml of ethyl acetate in two equal portions of 25ml each and this is added to the reaction mixture. The suspension is stirred at -14 to -15°C for an additional 30 minutes. A solution of above prepared N-

benzylmethylamine in 125ml of ethyl acetate is added at a constant rate, over a period of 40 minutes, while maintaining an internal temperature of -14 to -15°C. The addition funnel is washed with 50ml of ethyl acetate in two equal portions of 25ml each and this is added to the reaction mixture. After stirring at the same temperature for an additional 1 hour, a solution of 34.4ml (36.22g) of isobutyl chloroformate in 25ml of ethyl acetate is added over a period of 10 minutes while maintaining an internal temperature of -14 to -16°C. The addition funnel is washed with 10ml of ethyl acetate in two equal portions of 5ml each and this is added to the reaction mixture. The suspension is stirred at -14 to -16°C for an additional 15 minutes. A solution of 37.4g of N-benzylmethylamine (pretreated with 1.5g of ethyl trifluoroacetate as above) in 25ml of ethyl acetate is added at a constant rate, over a period of 10 minutes, while maintaining an internal temperature of -14 to -15°C. The addition funnel is washed with 10ml of ethyl acetate in two equal portions of 5ml each and this is added to the reaction mixture. The reaction mixture is warmed to room temperature (21-22°C) over a period of 1 hour. The reaction mixture is stirred at room temperature (21-22°C) for an additional 1 hour. 2.5 L of water are added and stirring is continued for 5-10 minutes. The organic layer is separated and washed with 1.876 L of 1N hydrochloric acid followed by 1.8 L of water. The organic layer is washed with 1.5 L of 5% aqueous sodium bicarbonate. The resulting organic layer is washed with 1.5 L of water, followed by 1.0 L of brine and filtered in a Buchner funnel with suction to obtain 6.1 L of a solution of Boc-(S)-3-(2-naphthyl)alanyl-N-benzyl-N-methylamide in ethyl acetate. This solution is held overnight at room temperature under nitrogen for the next step.

STEP II (≡ EXAMPLE 1B)

A 12-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, drying tube, and cooling bath is charged with a solution of 455.75g of hydrochloric acid gas in 2.2 L of ethyl acetate. The solution is

cooled to 10°C (internal temperature) and 6.1 L of the crude product of STEP I in ethyl acetate is added over a period of 25 to 30 minutes while maintaining an internal temperature below 20°C. The mixture is warmed to room temperature (22-23°C) and stirred at this temperature for an additional 3 hours. The reaction mixture is concentrated under reduced pressure (40-45°C, 100 to 110 mm Hg) until 5.0 L of solvent is collected, cooled to 20-22°C and stirred for 15-30 minutes. The solid is collected by filtration in a Buchner funnel with suction and the solid washed with a total of 1.2 L of ethyl acetate in four equal portions of 300 ml each. The solid is dried at 50-55°C (762mm Hg) for 24 hours to obtain a constant weight of pure (S)-3-(2-naphthyl)alanyl-N-benzyl-N-methylamide hydrochloride. Purity: 98.4% (by HPLC); $[\alpha]_D$: +24.8° (c=1,methanol).

STEP III (≡ EXAMPLE IC)

A 5-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, and cooling bath is charged with 332.0 g of the product of STEP II and 2.0 L of isopropyl acetate. The suspension is cooled to 10-12°C (internal temperature) using an ice-water bath. 1.4 L of 5% aqueous sodium hydroxide are added with efficient stirring over a period of 10 minutes while maintaining an internal temperature of 10-12°C. The mixture is warmed to 21-22°C in 30 minutes. The organic layer is separated and washed with 0.7 L of water followed by 0.25 L of brine. The organic layer is dried over 100g of anhydrous sodium sulfate and filtered in a Buchner funnel with suction. The solids are washed with a total of 90 ml of isopropyl acetate in three equal portions of 30 ml each. The organic layer is concentrated under reduced pressure (40-100mbar; 43-45°C) until no further solvent distills to obtain 0.35 L of (S)-3-(2-naphthyl)alanyl-N-benzyl-N-methylamide (free base) as an oil. This is held.

A 12-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet-outlet, and cooling bath is charged with 205.4g

of Boc-(S)-proline, and 3.2 L of ethyl actate. The mixture is stirred for 5 minutes to obtain a solution. 125.6g of 4-methylmorpholine are added over a period of 10 minutes while maintaining an internal temperature of 20-22°C. The addition funnel is washed with 25 ml of ethyl acetate and this is added to the reaction mixture. The solution is cooled to -15°C (internal temperature) and a solution of 132.9g of isobutyl chloroformate in 75 ml of ethyl acetate is added over a period of 25 to 30 minutes while maintaining an internal temperature of -14 to -16°C. The addition funnel is washed with 60 ml of ethyl actate in three equal portions of 20ml each and this is added to the reaction mixture. The suspension is stirred at -14 to -15°C for an additional 30-35 minutes. A solution of the previously prepared 0.35 L of (S)-3-(2-naphthylalanyl-N-benzyl-N-methylamide in 0.35 L of ethyl actate is added at a constant rate of ~10 ml/minute over a period of 70 minutes while maintaining an internal temperature of -14 to -15°C. The addition funnel is washed with a total of 75 ml of ethyl acetate in three equal portions of 25 ml each and this is added to the reaction mixture. The reaction mixture is warmed to room temperature (21-22°C) over a period of 1 hour. The reaction mixture is stirred at room temperature (21-22°C) for an additional 1 hour. 3.0 L of water are added at 21-23°C and the whole is stirred for 5-10 minutes. The organic layer is seprated and washed with 1.5 L of 1N hydrochloric acid followed by 1.5 L of water. The resulting organic layer is washed sequentially with 1.5 L of 5% aqueous sodium bicarbonate, 1.5 L of water, and 1.0 L of brine. The organic layer is filtered in a Buchner funnel with suction to obtain 3.93 L of a solution of Boc-(S)-prolyl-(S)-3-(2-naphthyl)alanyl-N-benzyl-N-methylamide. This solution is held overnight at room temperature under nitrogen for the next step.

STEP IV (≡ EXAMPLE IC)

A 12-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, drying tube, and cooling bath is charged with a solution of 337.3g of

hydrochloric acid gas in 1.63 L of ethyl acetate. The solution is cooled to 6°C (internal temperature) and 3.93 L of the crude product solution of STEP III is added over a period of 25 to 30 minutes while maintaining an internal temperature below 20°C. The addition funnel is washed with a total of 180 ml of ethyl acetate in three equal portions of 60ml each and this is added to the reaction mixture. The mixture is warmed to room temperature (22-23°C) and stirred at this temperature for an additional 2 hours. The reaction mixture is concentrated under reduced pressure (40-44°C, 80 to 110mm Hg) until 4.7 L of solvent is collected. The resulting 0.66 L of an oil is dissolved in 1.4 L of water and extracted with 1.0 L of ethyl acetate. The organic layer is extracted with 0.2 L of water. The aqueous layers are combined and transferred to a 5-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, and colling bath. The aqueous layer is cooled to 15°C (internal temperature) using an ice-water bath and a precooled solution (20-21°C) of 120g of sodium hydroxide in 1.2 L of water is added to it over a period of 20-30 minutes while maintaining an internal temperature below 18°C (pH should be 9-10). The mixture is warmed to room temperature (21-23°C) in 10 minutes and extracted with 3.0 L of isopropyl acetate. The organic layer is separated and the aqueous layer extracted with a total of 1.0 L of isopropyl acetate in two equal portions of 0.5 L each. The combined organic layers are washed with 0.75 L of water followed by 0.5 L of brine. The organic layer is dried over 125g of anhydrous soldium sulfate and filtered in a Buchner funnel with suction. The solids are washed with a total of 100ml of isopropyl acetate in two equal portions of 50ml each to obtain 5.02 L of (S)-prolyl-(S)-3-(2-naphthyl)-alanyl-N-benzyl-N-methylamide. This solution is held under nitrogen for the next step.

STEP V (≡ EXAMPLE 1)

A 12-l, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet-outlet, and cooling bath is charged with 5.02 L

of a solution of the product of STEP IV in isopropyl acetate. The solution is cooled to 10-11°C (internal temperature) in an ice-water bath (bath temperature 6-7°C) and a solution of 156g of 2-nitrophenyl isocyanate in 0.5 L of isopropyl acetate is added over a period of 20 to 30 minutes while maintaining an internal temperature below 17-18°C. The addition funnel is washed with a total of 50 ml of isopropyl acetate in two equal portions of 25ml each and this is added to the reaction mixture. The mixture is warmed to room temperature (22-23°C) and stirred at this temperature for an additional 1 hour. The reaction mixture is filtered and concentrated under reduced pressure (40-45°C, 70 to 100mm Hg) until no more solvent distills. The ~0.64 kg of crude product is dissolved in 0.5 L of ethyl acetate/hexane mixture (60:40 v/v) by heating at 40°C (bath temerpature), cooled and loaded onto a chromatography column containing 8.5 kg of silica gel. The column is eluted until the liquid level reaches the silica gel. The flask is washed with a total of 0.9 L of ethyl acetate/hexane mixture (60:40 v/v) in three equal portions of 0.3 l each and loaded onto the column. Each time the column is eluted until the liquid level reaches the silica gel. The column is eluted with 36.5 L of ethyl acetate/hexane mixture (60:40 v/v) and then with 38 L of ethyl acetate. Fractions 16-24 containing the product are combined and solvents evaporated (39-44°C, 70-110mm Hg) until no solvent distills. The resulting oil is suspended in 1.8 L of ethanol (190 proof) and solvents evaporated (39-44°C, 70-110mm Hg). The residue is dissolved in 3.1 L of ethanol (190 proof) by heating (bath temperature 40-45°C). The resulting 3.6 L solution is cooled to 29-30°C (internal temperature) and added to 13 L of water, which is precooled to 7-8°C (internal temperature, bath temperature is 0 to -2°C) in a 12-L, 4-necked, round-bottomed flask, equipped with a mechanical stirrer, digital thermometer, addition funnel, nitrogen inlet-outlet, and cooling bath, over a period of 30 minutes while maintaining an internal temperature of 7-9°C. The addition funnel is washed with a total of 10 ml of ethanol (190 proof) in two equal portions of 50 ml each and this is added to the suspension. The suspension is stirred at the same temperature

for an additional 35 minutes and the solid collected by filtration over a polypropylene pad filter in a Buchner funnel with suction. The solid is washed with a total of 3 L of water in three equal portions of 1 L each. The solid is dried in a kilo plant SS-vacuum tray dryer on a polyethylene liner sheet in a tray at 42-43°C (6.18 psia or ca. 319mm Hg) to obtain a constant weight (44 hours) of the product compound 2-nitrophenylcarbamoyl-[(S)-prolyl]-[(S)-3-(2-naphthyl)alanyl]-N-benzyl-N-methylamide as a yellow solid. Purity: 99.4% (by HPLC 951068) $[\alpha]^{20}_{D}$: -59.8° (c=1,methanol).

Compounds of formula I and their pharmaceutically acceptable acid addition salts, hereinafter referred to collectively as "AGENTS OF THE INVENTION", exhibit tachykinin antagonist activity. More particularly AGENTS OF THE INVENTION exhibit potent antagonist activity at the NK-1 tachykinin (substance P) receptor. AGENTS OF THE INVENTION are accordingly useful as pharmaceuticals, e.g. as hereinafter further set forth.

Binding affinity for the NK-1 receptor may be demonstrated by ability to displace [3H]-substance P binding, e.g. as indicated by the following test method:

TEST I

Displacement of [^{3}H]-substance P binding from mebranes from Cos-7 cells transfected with cloned human NK-1 receptor (hNK-1R).

Preparation of membranes containing hNK-1R

Transient expression of recombinant DNA in Cos-7 cells and the subsequent harvesting of the cells is performed analogously to standard techniques (Sambrook et al., 1989; Kriegler 1990).

Membranes are prepared from the transfected Cos-7 cells by homogenisation at 10 000 rpm for 30 seconds, using a Kinematica homogeniser. The resultant suspension is centrifuged for 30 min.

at 28 000 xg. The pellet is washed a further two times by resuspension in Tris-HCl (50 mM, pH 7.4) and re-centrifugation. The final pellet is resuspended at 2-8 mg protein/ml in Tris-HCl (50 mM, pH 7.4), containing 5% glycerol and 500 µl aliquots are frozen rapidly on dry-ice.

[^{3}H] Substance P binding to hNK-1R receptor containing membranes

Membranes prepared as above are maintained in suspension at -70°C. Binding assays are performed in 1.2 ml micronic polypropylene tubes containing in a final volume of 0.5 ml: binding buffer (composition in μgm^{-1}: chymostatin, 2; leupeptin, 4; bacitracin, 40, 2mM $MnCl_2$, 0.1% bovine serum albumin, 20mM Hepes, pH7.4); 400µl membrane suspension (0.019 ± 0.003 mg protein per tube); 50 µl 6 nM [^{3}H]Substance P and 50 µl 50% dimethyl sulfoxide (to define total), 50µl CP96,345 (Snider et al., 1991) (10µM) (to define non-specific binding) or 50 µl concentration of test compound at varying. 10 mM stocks are made of test compounds in 100% dimethyl sulfoxide (DMSO). This stock is further diluted to 1mM in 50% DMSO before use. Six concentrations of each test compound are used to give inhibition curves. All assays are done in triplicate. Specific binding to NK1 receptors is defined as the difference between that found in total bound tubes and that found in non specific binding tubes. Reaction is initiated with the addition of the radioligand and incubated at 24°C for 45 minutes. Reaction is terminated by the addition of 500µl of ice cold Tris-HCl buffer (50 mM, pH 7.4). The binding mixture is rapidly filtered over Whatman GF/B filter sheets (pre-soaked in 0.3% polyethyleneimine for 2-3 hours at room temperature). The tubes and filters are washed 6 times with 1ml of ice cold wash buffer. Radioactivity bound to the filters is estimated using liquid scintillation in a Canberra Packard TopCount. Microscint-40 is the liquid scintillant used. Binding parameters are calculated by the method of Munson and Rodbard, 1980 using LIGAND.

Initial protein experiments with human NK-1 receptor transfected

Cos-7 cell membranes show that the specific binding of [^{3}H] Substance P increase in parallel with protein concentration up to 80-100 µg/assay tube. Routinely the protein concentration is 19 ± 3 µg/assay tube. At this concentration, the specific binding of [^{3}H] Substance P is routinely >70% of total binding and 3% of total radioactivity added to the incubation medium.

The association of [^{3}H] Substance P to human NK1 receptor/Cos-7 membranes is rapid, reaching equilibrium at 20 min. and being stable upto 90 min. at room temperature. Binding is measured at 45 minutes in all subsequent assays.

Saturation curves for [^{3}H] Substance P binding to human NK1 receptor/Cos-7 cell membranes are measured after 45 min. of incubation at room temperature. The equilibrium dissociation constant (K_D = 85 ± 12 pM) and number of binding sites (B_{max} = 537 ± 139), is estimated by non-linear iterative curve-fitting of at least three data sets, simultaneously, for each transfection, using LIGAND (Munson et al., 1980) and the arithmetic mean calculated across all ten transfections.

References:

Kriegler et al. (1990): Gene Transfer and Expression. A laboratory manual, Stockton Press.
Munson et al. (1980): Anal. Biochem. 107:220.
Sambrook et al.: (1989) Molecular Cloning: A laboratory manual (2nd edition), Cold Spring Harbour Laboratory Press. Refs.
Snider et al. (1991): Science 251: 435-436.

AGENTS OF THE INVENTION are active in displacing [^{3}H] Substance P in this test method at concentrations of the order of from Ki = about 0.01 to about 10.0 nM.

Pharmacological, e.g. analgesic, utility of AGENTS OF THE INVENTION as NK-1 receptor antagonists can also be demonstrated in accordance with standard test models for examples as follows:

TEST II: HYPERALGESIA MODEL

Test groups of 6 male Dunkin-Hartley guinea pigs (ca. 250g) receive 100µl of 1% carrageenan injected intraplantar. Mechanical hyperalgesia is measured employing a Ugo Basile Analgesymeter (250g max. applied to the paw) and the withdrawal threshold determined as the first signs of distress in the animal. Thermal hyperalgesia is determined by placing animals in a perspex box, applying ramp heat stimulus to the plantar surface of the paw and measuring the latency to paw withdrawal [Hargreaves et al., Pain 32, 77-88 (1988)]. Withdrawal thresholds to mechanical and thermal stimuli are measured in both inflamed and non-inflamed paws.

Thermal/mechanical hyperalgesia is measured 24 hours after carrageenan injection. Test substance, i.e. AGENT OF THE INVENTION in 10% DMSO in tragacanth (1%), is then administered p.o. at varying dosage and thermal/mechanical hyperalgesia re-measured after a further 3 hours.

In the above test method AGENTS OF THE INVENTION are found to be active in reducing mechanical hyperalgesia at dosages of the order of from about 0.1 to about 5.0 mg/kg p.o. and thermal hyperalgesia at dosages of the order of from about 0.5 to about 5.0 mg/kg p.o..

AGENTS OF THE INVENTION are accordingly useful as pharmaceuticals, e.g. as tachykinin particularly NK-1 (substance P), antagonists, e.g. for the treatment of diseases or clinical conditions characterised by or having an aetiology comprising excessive or undesirable substance P mediated activity.

In particular they are useful as analgesics or anti-nociceptive agents for the treatment of pain of various genesis or aetiology. They are also useful as anti-inflammatory or anti-oedemic agents for the treatment of inflammatory reactions, diseases or conditions.

In relation to their analgesic activity and in contrast with other tachykinin, e.g. NK-1, antagonists known from the art, AGENTS OF THE INVENTION have surprisingly been found to have marked or enhanced activity following oral administration. They have also and in contrast with other tachykinin, e.g. NK-1, antagonists known from the art, been found to have marked anti-nociceptive action upon the central nervous system following systemic administration, i.e. they readily penetrate the CNS.

Having regard to their analgesic/anti-inflammatory profile, AGENTS OF THE INVENTION are in particular useful for the treatment of inflammatory pain, hyperalgesia and, especially chronic pain, e.g. severe chronic pain. They are, for example useful for the treatment of pain, inflammation and/or oedema consequential to trauma, e.g. burns, sprain, fracture or the like, as well as surgical intervention, e.g. for the treatment of post-operative pain. They are further useful for the treatment of inflammatory pain of diverse genesis, e.g. for the treatment of arthritis and rheumatic diesease, teno-synovitis, vasculitis, and rheumatic joint pain, e.g. rheumatid arthritis, as well as for the treatment of gout.

AGENTS OF THE INVENTION are further useful for the treatment of pain associated with angina, renal or billiary colic and menstruation.

AGENTS OF THE INVENTION are also useful for the treatment of pain associated with migraine. They are further useful as anti-ematic agents, for the treatment of emesis, e.g. emesis consequential to chemotherapy, poisons, pregnancy or migraine, as well as for the treatment of incontinence and gastrointestinal disorder such as retard emptying of the stomach, dyspepsia, esophageal reflux and flatulence.

AGENTS OF THE INVENTION are further useful in the treatment of chronic or obstructive airways disease, e.g. for the control or prevention of bronchial oedema, pulmonary mucosal secretion or

airways hyperreactivity, e.g. for use as therapeutic or prophylactic agents in the treatment of asthma. AGENTS OF THE INVENTION are useful for the treatment of atopic and non-atopic asthma, e.g. for the treatment of allergic asthma, exercise induced asthma, occupational asthma, asthma following bacterial infection and drug-induced, e.g. asprin induced, asthma as well as of wheezy infant syndrome.

Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and, in particular, byssinosis.

Yet further inflammatory or obstructive airways diseases and conditions for which the ACTIVE AGENTS may be used include adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary or airways disease (COPD or COAD), and bronchitis. ACTIVE AGENTS may also be used for the treatment of allergic and vasomotor rhinitis.

AGENTS OF THE INVENTION are further indicated for use in the treatment of

- disorders of the central nervous system, in particular anxiety states, for example in the treatment of anxiety, depression, psychosis, schizophrenia, panic attack, phobias such as agrophobia, stress related somatic disorders and addiction disorders such as alcoholism or cocaine abuse;

- neurodegenerative disorders such as dementia, including senile dementia, Alzheimer's disease and Down's syndrome;

- demyelinating diseases such as MS, ALS and other neuropathological disorders, for example peripheral

neuropathy, e.g. diabetic and chemotherapy induced neuropathy;

AGENTS OF THE INVENTION are yet further indicated for use in the treatment of diseases or conditions associated with dysfunction of the immune system, e.g. autoimmune diseases, in particular where these are associated with inflammatory, oedemic or nociceptive event. Particular diseases or conditions in this category include, for example autoimmune haematological disorders (including e.g. haemolytic anaemia, aplastic anaemia, pure red cell anaemia and idiopathic thrombocytopenia), systemic lupus erythematosus, polychondritis, sclerodoma, Wegener granulamotosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, psoriasis, Steven-Johnson syndrome, idiopathic sprue, autoimmune inflammatory bowel disease (including e.g. ulcerative colitis and Crohn's disease) endocrine ophthalmopathy, Graves disease, sarcoidosis, multiple sclerosis, primary billiary cirrhosis, juvenile diabetes (diabetes mellitus type I), uveitis (anterior and posterior), keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriasis, psoriatic arthritis and glomerulonephritis (with and without nephrotic syndrome, e.g. including idiopathic nephrotic syndrome or minimal change nephropathy) as well as vasculitis. AGENTS OF THE INVENTION may also be useful as immuno-suppressant or immunosuppressive adjuvents, e.g. for use in conjunction with other immunosuppressive, e.g. cyclosporin or immunosuppressive macrolide therapy, for the suppression of allograft rejection, for example following allogenic e.g. allogenic kidney, liver, corneal, heart, lung or heart-lung transplantation.

AGENTS OF THE INVENTION are yet further indicated for use in the treatment of allergic diseases or conditions, e.g. of the skin, eye, naso-pharynx or gastro intestinal tract, in particular where such disease or condition is associated with inflammatory, oedemic or nociceptive reactions. Examples of such diseases or conditions include, for example, exzema, hypersensitivity disorders such as poison ivy allergy, contact dermatitis, conjunctivitis, vernal conjunctivitis, keratoconjunctivitis

sicca, urtharia and other eczemoid dermatoses.

AGENTS OF THE INVENTION are also useful in the treatment of disorders of blood flow caused by vasodilation and vasospastic diesease such as angina, migraine and Reynaud's disease.

In addition to the foregoing AGENTS OF THE INVENTION have also been found to possess P-glycoprotein blocking activity. AGENTS OF THE INVENTION are accordingly further indicated for use as adjuvent or co-therapy with drug substances of other therapeutic category for example:

- for increasing or enhancing effectiveness of, or increasing or enhancing sensitivity to, other chemotherapeutic drug therapy, in particular anti-microbial (e.g. anti-bacterial, anti-viral, antifungal or anti-protozoal) chemotherapy, chemotherapy for AIDS and, especially, anti-cancer or anti-tumor (e.g. anti-neoplastic or cytostatic) chemotherapy. They are accordingly indicated for use, e.g. as a means of reducing regular chemotherapeutic dosage levels, for example, in the case of anti-neoplastic or cytostatic drug therapy, as a means of decreasing overall drug toxicity and, more especially, as a means of reversing or reducing resistance, including both inherent and acquired resistance, to chemotherapy;
- to enable or potentiate other drug therapy directed at the central nervous system, e.g. to enhance drug penetration of the blood-brain barrier, for example to enable, increase or enhance other psychotropic drug therapy, e.g. for administration in conjunction with other analgesic or psychomotor stimulatory or depressant agents or agents, for example, for treatment of neurodegenerative disease including Parkinson's disease, Alzheimer's disease and so forth as well as chemotherapy to be directed at tumor of the brain;
- as antiparasitic, particularly antiprotozoic, agents, e.g., particularly against organisms of the genera Toxoplasma (e.g., Toxoplasma gondii) and Plasmodia (e.g., Plasmodium falciparum).

For the above indications the dosage of AGENTS OF THE INVENTION will, of course, vary depending upon, for example, the host, the mode of administration and the nature and severity of the condition being treated as well as the relative potency of the particular AGENT OF THE INVENTION employed. However, in general, satisfactory results in animals, e.g. for the treatment of pain, migraine and emesis, are indicated to be obtained at daily dosages of from about 0.1 to about 10 mg/kg p.o.. In larger mammals, for example humans, an indicated daily dosage is in the range of from about 7.0 to about 700 mg/day p.o., e.g. ca. 100mg/day p.o. conveniently administered once or in divided doses up to 4 x per day or in sustained release form, e.g. for the treatment of pain, migraine and emesis. Oral dosage forms accordingly suitably comprise from about 1.5 to about 150 or 700 mg e.g. from about 25 to 100 mg AGENT OF THE INVENTION admixed with an appropriate pharmaceutically acceptable diluent or carrier therefor.

Having regard to their relatively low solubility AGENTS OF THE INVENTION for oral administration are suitably formulated in a composition comprising a hydrophilic phase (e.g. propylene glycol/ethanol) a hydrophobic phase (e.g. vegetable oil mono-di-triglycerides such as commercially available under the registered trade mark MAISINE) and a surfactant (e.g. a polyoxyhydrogenated vegetable oil such as commercially available under the registered trade mark CREMOPHOR). Formulations for i.v. administration may be prepared by dissolution of the selected AGENT OF THE INVENTION in ethanol together with an appropriate surfactant, e.g. CREMOPHOR RH 40. The following example is illustrative of the preparation of galenic forms suitable for oral administration:

COMPONENT	QUANTITY/UNIT DOSE
1. AGENT OF THE INVENTION, e.g. compound of EXAMPLE 1.	100.00 mg
2. Propylene glycol	94.70 mg
3. Corn oil-mono-di-triglycerides, e.g. MAISINE	319.90 mg

COMPONENT	QUANTITY/UNIT DOSE
4. Polyoxyl 40 hydrogenated castor oil, e.g. CREMOPHOR RH 40	383.70 mg
5. Ethanol, dehydrated	94.70 mg
Total	993.00 mg

Component 4 is warmed at 40°C until liquified. Components 2, 3 and 5 are added and the whole mixed in conventional manner until a clear solution is obtained. Component 1 in finely divided form, e.g. compound of EXAMPLE 1 (free base, amorphous) pin-milled, if required at low temperature, is added to the obtained solution and the whole mixed until a clear solution is obtained. The product is suitable for use as a solution for drinking. Alternatively the composition may be put up in soft or hard-gelatin encapsulated form, e.g. with each capsule containing 50 or 100mg component 1.

AGENTS OF THE INVENTION may alternatively be administered, e.g. topically in the form of a cream, gel or the like for example for the treatment of conditions of the skin as hereinbefore described or by inhalation, e.g. in dry powder form, for example for the treatment of obstructive or inflammatory airways disease, or by any other appropriate route, e.g by injection or infusion.

The preferred AGENT OF THE INVENTION is the product or EXAMPLE 1. In one series of experiments an established ED_{50} for this in TEST II above is of the order of 0.73 ± 0.09 mg/kg p.o. for mechanical hyperalgesia and of 1.75 ± 0.64 mg/kg p.o. for thermal hyperalgesia. An estimated ED_{50} for aspirin in the same test method is of the order of ca. 30 mg/kg for mechanical and ca. 100 mg/kg for thermal hyperalgesia. Indicated oral dosages for the EXAMPLE 1 compound as an analgesic agent will thus be of the order of 1/40th to 1/50th of those clinically employed using asprin.

A further preferred AGENT OF THE INVENTION is the product of EXAMPLE 17. In one series of experiments in accordance with TEST

II above the ED_{50} for this compound is found to be of the order of 1.0 mg/kg p.o. for mechanical hyperalgesia. Indicated oral dosages for the EXAMPLE 17 compound as an analgesic agent will thus be of the order of 1/30th of those clinically employed using aspirin.

In accordance with the foregoing the present invention also provides:

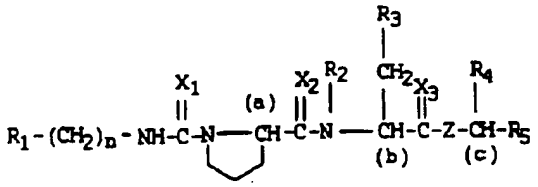
1) An AGENT OF THE INVENTION for use as a pharmaceutical, e.g. for use as an NK-1 (substance P) antagonist, for example for use in any of the particular indications hereinbefore set forth, in particular for use as an analgesic, anti-inflammatory or anti-oedemic agent or for use in treating allergic conditions or reactions, e.g. rhinitis, or in treating emesis;

2) A pharmaceutical composition comprising an AGENT OF THE INVENTION as active ingredient together with a pharmaceutically acceptable diluent or carrier therefor; and

3) A method for the treatment of any of particular indication hereinbefore set forth in a subject in need thereof which comprises administering an effective amount of an AGENT OF THE INVENTION to said subject.

CLAIMS

1. A compound of formula I



(I)

wherein

R_1 is phenyl mono- or di-substituted by one or two members selected from the group consisting of halogen, nitro, cyano, trifuloromethyl, hydroxy, methoxy, hydroxymethyl, methoxymethyl, methoxycarbonyl, carbamoyl and N-methylcarbamoyl,

n is zero or 1,

X_1 is oxygen, sulfur or =NCN,

X_2 and X_3 are each independently oxygen or sulfur,

R_2 is hydrogen or methyl,

R_3 is phenyl, halo-substituted phenyl, 2-naphthyl, IH-indol-3-yl or 1-methyl-indol-3-yl,

Z is $-N(CH_3)-$ or $-CH_2-$,

R_4 is phenyl, 3,5-bis(trifluoromethyl)phenyl or pyridyl and

R_5 is hydrogen, phenyl, 3,5-bis(trifluoromethyl)phenyl or pyridyl,

whereby, when X_3 is sulfur, Z is $-N(CH_3)-$,

or acid addition salt thereof.

2. A compound of formula I as illustrated in claim 1, wherein

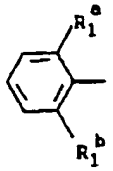
R_1 is 2-halo- or 2-nitro-phenyl,

n is zero,

X_2 and X_3 are each oxygen,

R_4 is phenyl or pyridyl,
R_5 is hydrogen, phenyl or pyridyl and
X_1, R_2, R_3 and Z have the meanings given in claim 1,
or acid addition salt thereof.

3. A compound of formula I as illustrated in claim 1, wherein R_1 is a group of formula



wherein
R_1^a is trifluoromethyl, halogen, methoxy or nitro and
R_1^b is hydrogen, trifluoromethyl, halogen, methoxy or nitro,
n is 1,
X_2 and X_3 are each oxygen,
R_3 is halo-substituted phenyl, 2-naphthyl, IH-indol-3-yl, or 1-methyl-indol-3-yl,
Z is $-N(CH_3)-$ and
X_1, R_2, R_4 and R_5 have the meanings given in claim 1,
or acid addition salt thereof.

4. A compound of formula I as illustrated in claim 1, wherein R_1 is 2-nitrophenyl, n is zero, X_1, X_2 and X_3 are each oxygen, R_2 is hydrogen, R_3 is 2-naphthyl, Z is $-N(CH_3)-$, R_4 is phenyl and R_5 is hydrogen.

5. A compound of formula I as illustrated in claim 1, wherein R_1 is 2-(methoxymethyl)phenyl, R_2 is hydrogen, n is zero, X_1, X_2 and X_3 are each oxygen, R_3 is 2-naphthyl, Z is $-N(CH_3)-$, R_4 is phenyl and R_5 is hydrogen.

6. A compound of formula I as illustrated in claim 1, wherein:
a) R_1 is 2-nitrophenyl, n is zero, X_2 and X_3 are each oxygen,

R_2 is hydrogen, R_3 is 2-naphthyl, Z is $-N(CH_3)-$ and
- X_1 is sulfur, R_4 is phenyl and R_5 is hydrogen,
- X_1 is =NCN, R_4 is phenyl and R_5 is hydrogen,
- X_1 is oxygen and R_4 and R_5 are each 2-pyridyl,
- X_1 is oxygen, R_4 is 2-pyridyl and R_5 is hydrogen, or
- X_1 is sulfur, R_4 is 2-pyridyl and R_5 is hydrogen; or

b) n is zero, X_1, X_2 and X_3 are each oxygen, R_2 is hydrogen, R_3 is 2-naphthyl, Z is $-N(CH_3)-$, R_4 is phenyl, R_5 is hydrogen and R_1 is 2-chlorophenyl, 4-nitrophenyl, 2-cyanophenyl, 3-cyanophenyl, 4-fluorophenyl, 2-(methoxycarbonyl)phenyl, 3-nitrophenyl, 2-(methylcarbamoyl)-phenyl, 2-carbamoylphenyl, 2-hydroxyphenyl or 2-hydroxymethylphenyl; or

c) R_1 is 2-nitrophenyl, n is zero, X_1, X_2 and X_3 are each oxygen, R_3 is 2-naphthyl, R_4 is phenyl, R_5 is hydrogen and

- R_2 is methyl and Z is $-N(CH_3)-$, or
- R_2 is hydrogen and Z is $-CH_2-$; or

d) R_1 is 2-nitrophenyl, n is zero, X_1, X_2 and X_3 are each oxygen, R_2 is hydrogen, R_3 is 2-naphthyl, Z is $-N(CH_3)-$, R_5 is hydrogen and R_4 is IH-indol-3-yl or 3,4-dichlorophenyl; or

e) n is 1, X_1 is sulfur, X_2 and X_3 are each oxygen, R_2 is hydrogen, R_3 is 2-naphthyl, Z is $-N(CH_3)-$, R_4 is phenyl, R_5 is hydrogen and R_1 is 2-chlorophenyl, 2-trifluoromethylphenyl, or 2-bromophenyl; or

f) R_1 is 2-chlorophenyl, n is 1, X_2 and X_3 are each oxygen, R_2 is hydrogen, R_3 is 2-naphthyl, Z is $-N(CH_3)-$, and
- X_1 is sulfur and R_4 and R_5 are each 2-pyridyl,
- X_1 is sulfur, R_4 is 2-pyridyl and R_5 is hydrogen,
- X_1 is oxygen, R_4 is phenyl and R_5 is hydrogen,
- X_1 is sulfur, R_4 is 3,5-bis(trifluoromethyl)phenyl and

R_5 is hydrogen, or

- X_1 is sulfur, and R_4 and R_5 are each phenyl; or

g) n is 1, X_1 is sulfur, X_2 and X_3 are each oxygen, Z is $-N(CH_3)-$, R_4 is phenyl, R_5 is hydrogen, and

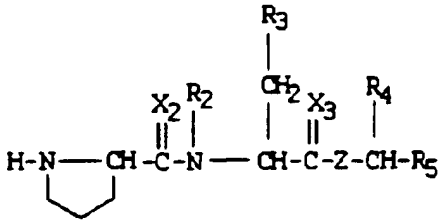
- R_1 is 2-nitrophenyl, R_2 is methyl and R_3 is 2-naphthyl,
- R_1 is 2-chlorophenyl, R_2 is hydrogen and R_3 is 3,4-dichlorophenyl or 1-methylindolyl-3-yl,

or acid addition salt thereof.

7. A compound of formula I as illustrated in claim 1, wherein the carbon atoms (a) and (b) and, when R_4 and R_5 are different and R_5 is other than hydrogen, the carbon atom (a) each have the (S)-configuration and wherein R_1 to R_5, X_1 to X_3, n and Z have the meanings given in any one of claims 1 to 3 or 6, or acid addition salt thereof.

8. A compound of formula I as illustrated in claim 1, wherein the carbonations (a) and (b) each have the (S)-configuration and wherein R_1 to R_5, X_1 to X_3, n and Z have the meanings given in claim 4 or 5.

9. A process for the production of a compound of formula I as defined in claim 1 or acid addition salt thereof which process comprises reacting a compound of formula II



(II)

wherein R_2 to R_5, X_2, X_3 and Z have the meanings given in claim 1, with a compound of formula III

$$R_1'-(CH_2)_n-N=C=X_1 \qquad (III)$$

wherein R_1' is phenyl, mono- or di-substituted by one or two members selected from the group consisting of halogen, nitro, cyano, trifluoromethyl, protected hydroxy, methoxy, protected hydroxymethyl, methoxymethyl or methoxycarbonyl, and n and X_1 have the meanings given in claim 1;
when required, deprotecting a compound thus obtained wherein R_1' is phenyl substituted by protected hydroxy and/or protected hydroxymethyl and/or transforming a compound thus obtained wherein R_1' is phenyl substituted by methoxycarbonyl to obtain a corresponding compound wherein R_1' is phenyl substituted by carbamoyl or N-methylcarbamoyl; and recovering the obtained compound of formula I in free or acid addition salt form.

10. A pharmaceutical composition comprising a compound of formula I as defined in any one of claims 1 to 8 or a pharmaceutically acceptable acid addition salt thereof together with a pharmaceutically acceptable diluent or carrier therefor.

11. A compound of formula I as defined in anyone of claims 1 to 8 or pharmaceutically acceptable acid addition salt thereof for use as a pharmaceutical.

12. A method for the treatment of pain or inflammation in a subject in need thereof which method comprises administering to said subject an analgesically or anti-inflammatorily effective amount of a compound as defined in any one of claims 1 to 8 or a pharmaceutically acceptable salt thereof.

INTERNATIONAL SEARCH REPORT

In. tional Application No
PCT/EP 95/04910

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/06 C07D207/16 A61K38/05 A61K31/40 //C07K7/22

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP,A,0 394 989 (FUJISAWA PHARMACEUTICAL CO., LTD.) 31 October 1990 * claim 1; page 3 * ---	1-12
A	WO,A,93 13065 (JAPAN TOBACCO INC.) 8 July 1993 -----	

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
18 April 1996	02. 05. 96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Hermann, R

INTERNATIONAL SEARCH REPORT

Information on patent family members

In tional Application No
PCT/EP 95/04910

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		CA-A-	2015359	28-10-90
		DE-D-	69015244	02-02-95
		DE-T-	69015244	04-05-95
		JP-A-	3027399	05-02-91
		US-A-	5164372	17-11-92
WO-A-9313065	08-07-93	JP-A-	5186498	27-07-93
		US-A-	5506256	09-04-96